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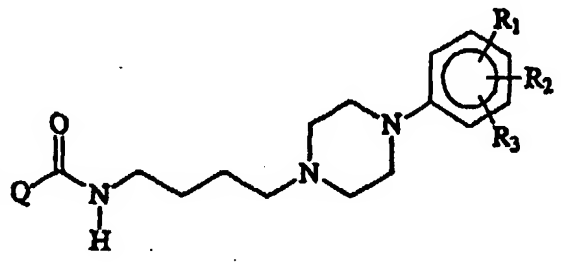
[Continued on next page]

(54) Title: 4-(4-SUBSTITUTED PIPERAZINYL-1YL)-BUTYLCARBOXAMIDES AS D3 DOPAMINE SUBTYPE SELECTIVE LIGANDS



(I)

(57) Abstract: The present invention relates to new D_3 dopamine receptor subtype selective ligands of Formula (I), wherein R_1, R_2 and R_3 independently represent substituents selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group, with the exception of compounds wherein a) $R_1 = R_2 = R_3 = H$, b) $R_1 = R_2 = H$ and $R_3 = C_{1-6}$alkoxy in the position 2 or R_3 is in the position 4 of the piperazinylphenyl moiety, c) R_1 ?= H and $R_2 = R_3 = C_{1-6}$alkoxy; Q represents an optionally substituted C_{1-6}alkyl, C_{1-6}alkenyl, phenyl or heteroaryl group.

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MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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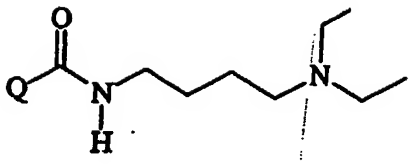
different substituents in the phenylpiperazine substructure. Due to this different substitution the compounds of the present invention have higher activity and selectivity for the D_3 receptors over the D_2 receptors.

Several phenylpiperazinylalkyl carboxylic acid amides are already described, however, the mechanism of action of the compounds described therein differ significantly from that of the compounds of the present invention: sedative activity (USP 3 005 821), analgesic and central nervous sytem depressant activity (FR 1 543 944), antipsychotic activity (USP 3 574 839), analgesic, antihistaminic and central nervous system depressant activity (FR 1 537 901), 5-HT_{1A} and 5-HT_2 receptor activity (JP 2000-204040 and WO 9903833), antitumor and immunosuppressive activities (DE 197 56 236), α_1-adrenergic and 5-HT_{1A} serotoninergic activity (USP 5 605 896), antagonists of NPY-induced feeding behavior (EP 747 356), 5-HT_{1A} antagonists (EP 395 313), antiallergic and antihistamine activity (USP 4 778 796), binary α,β-adrenergic blocking activities (USP 4 202 978), antihypertensive activity (FR 2 261 756), exhibiting an affinity for dopamine D_2 and 5-HT_{1A} receptors (EP 594 813), having ability to block apomorphine-induced climbing in mammals (EP 511 610) and antiagressive activity (EP 48 045). The compounds mentioned in these patent specifications are not declared having activity at dopamine D_3 receptors and this type of activity is not even suggested.

Summary of the invention

Surprisingly it has been found that, in contrast to the known above mentioned compounds of prior art, the new carboxamide derivatives of formula (I) of the present invention have high affinity at dopamine D_3 receptors and high selectivity over other receptors, especially dopamine D_2 receptors. Due to this high selectivity the undesired side effects of the compounds are much less pronounced.

The invention relates to new carboxamide derivatives of formula (I):



(I)

wherein

R_1, R_2 and R_3 independently represent substituents selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group,

with the exception of compounds wherein

a) $R_1 = R_2 = R_3 = H$,

b) $R_1 = R_2 = H$ and

$R_3 = C_{1-6}$ alkoxy in the position 2 or

R_3 is in the position 4 of the piperazinylphenyl moiety,

c) $R_1 = H$ and

$R_2 = R_3 = C_{1-6}$ alkoxy;

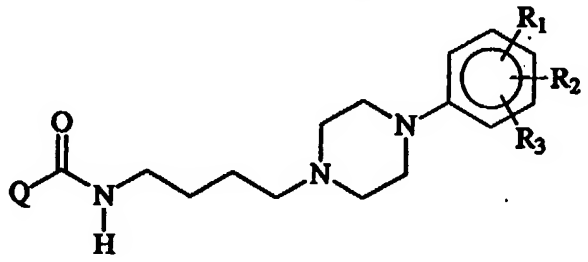
Q represents an optionally substituted C_{1-6}alkyl, C_{1-6}alkenyl, phenyl or heteroaryl group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the salts and/or hydrates and/or solvates thereof, to the processes for producing the same,to pharmacological compositions containing the same and to their use in therapy and/or prevention of psychoses (e.g. schizophrenia, schizo-affective disorders, etc.), drug (e.g. alcohol, cocaine and nicotine, opioids, etc.) abuse, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, amnesia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit

disorders, hyperactivity disorders in children, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesias) anxiety, sexual dysfunction, sleep disorders, emesis, aggression, autism, pain, ophthalmological diseases (e.g. glaucoma, etc.).

Detailed description of the invention

The invention relates to new carboxamide derivatives of formula (I):



(I)

wherein

R_1, R_2 and R_3 independently represent substituents selected from hydrogen, halogen, C_{1-6}alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group,

with the exception of compounds wherein

a) $R_1 = R_2 = R_3 = H$,

b) $R_1 = R_2 = H$ and

$R_3 = C_{1-6}$ alkoxy in the position 2 or

R_3 is in the position 4 of the piperazinylphenyl moiety,

c) $R_1 = H$ and

$R_2 = R_3 = C_{1-6}$ alkoxy;

Q represents an optionally substituted C_{1-6}alkyl, C_{1-6}alkenyl, phenyl or heteroaryl group;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the salts and/or hydrates and/or solvates thereof.

A heteroaryl ring in the meaning of Q may be monocyclic, bicyclic or tricyclic ring.

The monocyclic heteroaryl ring may be an optionally substituted 5- or 6-membered aromatic heterocyclic group.

The 5- and 6-membered heterocyclic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl and pyrazolyl, preferably pyridyl, thienyl, pyrimidinyl and pyrazinyl.

The bicyclic heteroaromatic group is indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 2,3-dihydro-3-oxo-4H-benoxazinyl, 1,2-dihydro-2-oxo-3H-indolyl, preferably quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl and indolyl group.

The tricyclic heteroaromatic group is β-carbolinyl.

R_1, R_2 and R_3 may be the same or different.

The substituents of C_{1-6}alkyl, C_{1-6}alkenyl, phenyl or heteroaryl groups in the meaning of Q are selected from hydrogen, halogen, hydroxy, cyano, amino, trifluoromethyl; C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, methylenedioxy, C_{1-6} alkylamino, C_{1-6}alkanoylamino, C_{1-6}alkylthio, optionally substituted aroyl, aryloxy, aminosulfonyl, arylsulfonylamido, optionally substituted mono or bicyclic aromatic or heteroaromatic ring,

with the exception of compounds of formula (I)

wherein Q = phenyl with one fluorine or chlorine substituent in any position, and

$R_1 = R_2 = H$, and

R_3 = trifluoromethyl in the position 3 of the piperazinylphenyl moiety.

The substituents of C_{1-6}alkanoyloxy in the meaning of R_1 are selected from hydrogen or halogen.

The amino, aminoalkyl, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl and sulfamoyl groups in the meaning of R_1, R_2 and R_3 may optionally be substituted on the N atom.

The mono or bicyclic heterocyclic group in the meaning of R_1, R_2 and R_3 may be saturated or unsaturated containing 1 to 4-heteroatoms selected from O, N or S.

In the compounds of formula (I) an alkyl group or an alkyl moiety in alkoxy, alkanoyl, alkanoylamino, alkanoyloxy groups may be straight or branched included methyl, ethyl, n-propyl, n-butyl, n-pentyl- n-hexyl and branched isomers thereof, such as isopropyl, t-butyl, sec-butyl, and the like.

The alkenyl moiety in the meaning of heteroalkenyl in Q may have 1 to 6 carbon atoms and 1 to 3 double bonds.

The halogen substituent(s) in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine, preferably fluorine, bromine and chlorine.

The invention relates also to the salts of compounds of formula (I) formed with acids.

Both organic and inorganic acids can be used for the formation of acid addition salts. Suitable inorganic acids can be for example hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid. Representatives of monovalent organic acids can be for example formic acid, acetic acid, propionic acid, and different butyric acids, valeric acids and capric acids. Representatives of bivalent organic acids can be for example oxalic acid, malonic acid, maleic acid, fumaric acid and succinic acid. Other organic acids can also be used, such as hydroxy acids for example citric acid, tartaric acid, or aromatic carboxylic acids for example benzoic acid or salicylic acid, as well as aliphatic and aromatic sulfonic acids for example methanesulfonic acid, naphtalenesulfonic acid and p-toluenesulfonic acid. Especially valuable group of the acid addition salts is in which the acid component itself is physiologically acceptable and does not have therapeutical effect in the applied dose or it does not have unfavourable influence on the effect of the active ingredient. These acid addition salts are pharmaceutically acceptable

acid addition salts. The reason why acid addition salts, which do not belong to the pharmaceutically acceptable acid addition salts belong to the present invention is, that in given case they can be advantageous in the purification and isolation of the desired compounds.

The different solvates and/or hydrates of compounds of formula (I) are also included within the scope of the invention.

Certain compounds of formula (I) can exist in the form of *cis*- and/or *trans*-isomers and/or stereoisomers and/or diastereomers. These are likewise within the scope of the present invention including all such isomers and the mixtures thereof.

As the invention relates also to the salts of compounds of formula (I) formed with acids, especially the salts formed with pharmaceutically acceptable acids, the meaning of compound of formula (I) is either the free base or the salt even if it is not referred separately.

Preferred compounds of the invention are those compounds of formula (I) wherein

$R_1 = R_2 = H$, and

R_3 represents halogen, C_{1-6}alkyl, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, optionally substituted amino, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group in the 2 or 3 position of the piperazinylphenyl moiety, or

$R_1 = H$,

R_2 and R_3 independently represent halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, optionally substituted amino, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic groups in the 2,3-, 2,4- or 3,5 positions of the piperazinylphenyl moiety,

whereby two adjacent groups of R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group; or

R_1, R_2 and R_3 independently represent halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, optionally substituted amino, aminocarbonyl or optionally substituted phenyl or naphthyl groups in the 2,3,4 positions of the piperazinylphenyl moiety, whereby two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group; and

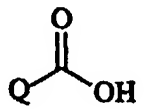
Q represents optionally substituted thienyl, pyridyl, pyrimidyl, pyrazinyl, quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl, indolyl, β-carbolinyl; C_{1-6}alkyl substituted by an optionally substituted aryl or heteroaryl group; C_{1-6}alkenyl substituted by an optionally substituted aryl or heteroaryl group; phenyl substituted by bromine, C_{1-6}(di)alkylamino, C_{1-6}alkyl, C_{1-6}alkoxy or optionally substituted aryl or heteroaryl group(s);

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the salts and/or hydrates and/or solvates thereof.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the salts and/or hydrates and/or solvates thereof as active ingredient.

Further subject of the present invention is the pharmaceutical manufacture of medicaments containing compounds of formula (I), as well as the process of treatments and/pr prevention with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

The present invention also provides a process for preparing compounds of formula (I) by forming an amide bond between a carboxylic acid of formula (II):

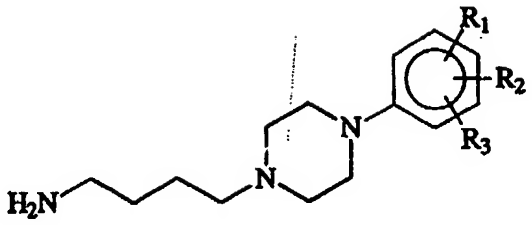


(II)

wherein the meaning of Q is as described above for the formula (I);

or derivatives thereof

and an amine of formula (III):



(III)

wherein the meanings of R_1, R_2 and R_3 are as described above for the formula (I);

or derivatives thereof.

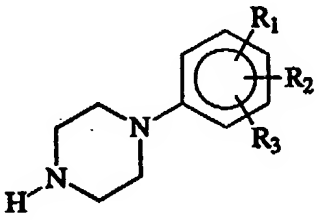
The amide bond formation may be carried out by known methods, preferably by preparing an active derivative from a carboxylic acid of formula (II) and this active derivative is reacted with an amine of formula (III) in the presence of a base.

The transformation of a carboxylic acid into an active derivative may be carried out in situ during the amide bond formation in a suitable solvent (for example dimethylformamide, acetonitrile, tetrahydrofurane, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (prepared for example from carboxylic acid with thionyl chloride), mixed anhydrides (prepared for example from carboxylic acid with isobutyl chloroformate in the presence of a base, e.g. triethylamine), active esters (prepared for example from carboxylic acid with hydroxybenztriazole and dicyclohexyl carbodiimide in the presence of a base e.g. triethylamine). The active derivatives can be prepared advantageously between -10°C and the reflux temperature of the solvent used. To the thus obtained solution or suspension an appropriate amine of formula (III) is added in a form of base or of a salt formed with organic or inorganic acid. The condensation reactions are followed by thin layer chromatography. The necessary reaction time is about 6-20 h. The work-up of the reaction mixture can be carried out by different methods. The products can be purified by known methods, for example by crystallization or by column chromatography. The structures of the products are determined by IR, NMR and mass spectroscopy.

Where they are not commercially available, the carboxylic acids of formula (II) may be prepared by procedures described in literature (e.g. 6-methoxybenzofuran-2-carboxylic acid: *J. Chem. Soc.* **1940**, 787; 6-methoxybenzothiazole-2-carboxylic acid: *J .Am. Chem. Soc.* **1963**, 85, 337; 5-methoxybenzothiophene-2-carboxylic acid: *J. Org. Chem.* **1961**, 26, 1326; 4-imidazo[1,2-a]pyridin-2-yl-benzoic acid: WO 9534540; 4-(pyrimidin-4-yl)-benzoic acid: WO 9957113; 9H-β-carboline-3-carboxylic acid: *Heterocycles* **1998**, 48, 993) or by procedures analogous to those described in literature. The compounds of formula (II) are either known or capable of being prepared by various methods known in the art.

The syntheses of some commercially not available carboxylic acids of formula (II) are described in the Examples.

The amines of formula (III) may be prepared by alkylation of compounds of formula (IV):



(IV)

wherein the meaning of R_1, R_2 and R_3 are as described above for formula (I);

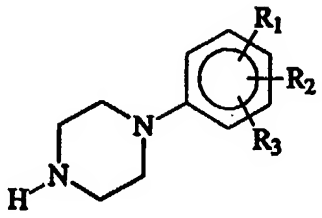
by standard methods.

Thus for example compound (IV) may be reacted with N-(4-bromobutyl)phthalimide followed by the removal of the phthaloyl group to give compound (III) or, where R_1, R_2 and R_3 are indifferent towards reducing agents, by alkylation with 4-bromobutyronitrile followed by reduction of the cyano group.

Where they are not commercially available, the piperazines of formula (IV) may be prepared by known methods. Thus a properly substituted aniline may be reacted with bis-(2-hydroxy-ethyl)amine and aquaeous hydrobromic acid (e.g. USP 2 830 056), with bis-(2-chloro-ethyl)amine hydrochloride (e.g. *J. Med. Chem.* **1997**, 40, 2674) or with bis-(2-bromo-ethyl)amine (e.g. *Collect. Czech. Chem. Commun.* **1934**, 211). An other procedure may be the reaction of a properly

substituted arylhalogenide with piperazine (e.g. *J. Med. Chem.* 1989, 32, 1052; *Tetrahedron Lett.* 1999, 40, 5661).

The piperazine derivatives of formula (IV):



(IV)

wherein

R_1 and R_2 are the same or different and represent hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl; hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1 and R_2 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group, and

R_3 is optionally substituted phenyl,

excluding when

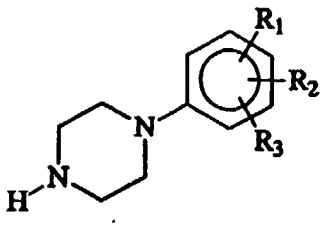
$R_1 = R_2 = H$;

are new.

These compounds and/or salts and/or hydrates and/or solvates thereof are also included within the scope of the present invention.

The new piperazine derivatives of formula (IV), wherein R_1, R_2 and R_3 have the same meaning as defined above, and/or salts and/or hydrates and/or solvates thereof may be prepared by various methods known in the art. One of them is as follows:

protecting the secondary amine of a piperazin derivative of formula (IV):



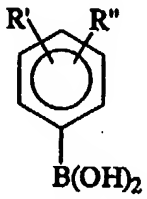
(IV)

wherein

R_1 and R_2 are as defined above, and

R_3 is halogen;

followed by reacting the compound obtained with a compound of formula (VII):



(VII)

wherein

R' and R" are the same or different and represent hydrogen, halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyloxy, amino or alkyl amino;

in the presence of a catalyst applied usually in Suzuki coupling and a base; and

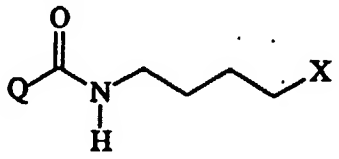
finally by deprotecting the piperazine derivative obtained; and

thereafter optionally forming a salt and/or hydrate and/or solvate of formula (IV), wherein R_1, R_2 and R_3 are as defined above.

The process for producing new piperazine derivatives of formula (IV) are also included within the scope of the present invention.

The piperazines of formula (IV) are key intermediates for producing acid amide derivatives exhibiting selective dopamine D_3 receptor activity. The use of piperazines of formula (IV) as intermediates for producing acid amide derivatives exhibiting selective dopamine D_3 receptor activity is also included within the scope of the present invention.

The compounds of formula (I) can also be obtained by the reaction of a compound of formula (IV) or derivatives thereof with a compound of formula (V):

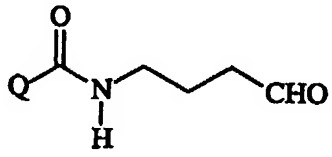


(V)

wherein Q has the meaning as defined in carboxamide derivatives of formula (I) and X is a so-called leaving group, preferably chlorine, bromine, iodine, tosylate or mesylate or derivatives thereof.

The reaction may be carried out in an inert solvent, for example, acetone, dimethylformamide and acetonitrile in the presence of a base (e.g. sodium hydrogencarbonate or potassium carbonate). The reaction temperature is usually between room temperature and the reflux temperature of the solvent used, and the reaction time varies from a few hours to approximately 20 hours.

The compounds of formula (I) may also be obtained by the reaction of a compound of formula (IV) or derivatives thereof with a compound of formula (VI):



(VI)

wherein Q has the meanings defined in carboxamide derivatives of formula (I); or derivatives thereof

under the circumstances of reductive amination.

The reaction may be carried out in an inert solvent (e.g. chlorinated hydrocarbons, alkanols or ethers) in the presence of a reductive agent, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The reaction temperature is usually between 0°C and room temperature. The necessary reaction time is about 2-24 h.

The obtained carboxamide derivatives of formula (I) – independently from the method of preparation – in a given case can be transformed into an other compound of formula (I) by introducing further substituent(s) and/or modifying

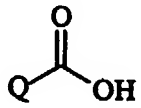
and/or removing the existing one(s), and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base. For example cleaving the methyl group from a methoxy group leads to phenol derivatives. The cleavage of methyl group can be carried out, e.g. with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group can be transformed into acyloxy or sulfonyloxy derivatives thereof with different acylating or sulfonylating agents. The reactions may be carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (e.g. triethylamine or sodium carbonate). The compounds of formula (I) containing cyano groups can be, e.g. transformed to amides by hydrolysis with hydrogenperoxide in dimethylsulfoxide, or to amidines via forming iminoester with gaseous hydrochloric acid in ether, followed by treatment with ammonia, etc.

Those having skill in the art will recognize that the starting materials may be varied and additional steps can be employed to produce compounds encompassed by the present invention, as demonstrated by the Examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

The carboxamide derivatives of formula (I) can also be prepared on solid support in the following way.

A protected 4-aminobutanol derivative e.g. triisopropylsilanyloxy-butylamine is attached to a polystyrene resin e.g. 4-formyl-3-methoxy-phenoxy polystyrene by reductive amination, e.g. with $NaB(OAc)_3H$ or $NaBH_3CN$ (i),

followed by acylation the amino group with a carboxylic acid of formula (II):



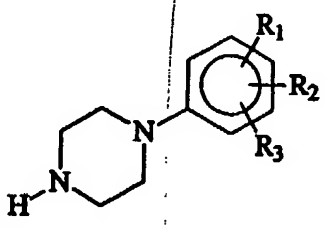
(II)

wherein Q is the same as defined above for the formula (I); or derivatives thereof (ii),

removing the protective group (iii),

the terminal free hydroxyl group is converted into halogenide, preferably iodide or bromine, with a halogenation agent e.g. PPh_3Br_2, PPh_3I_2, preferably PPh_3I_2 (iv),

the amine derivatives of formula (IV):



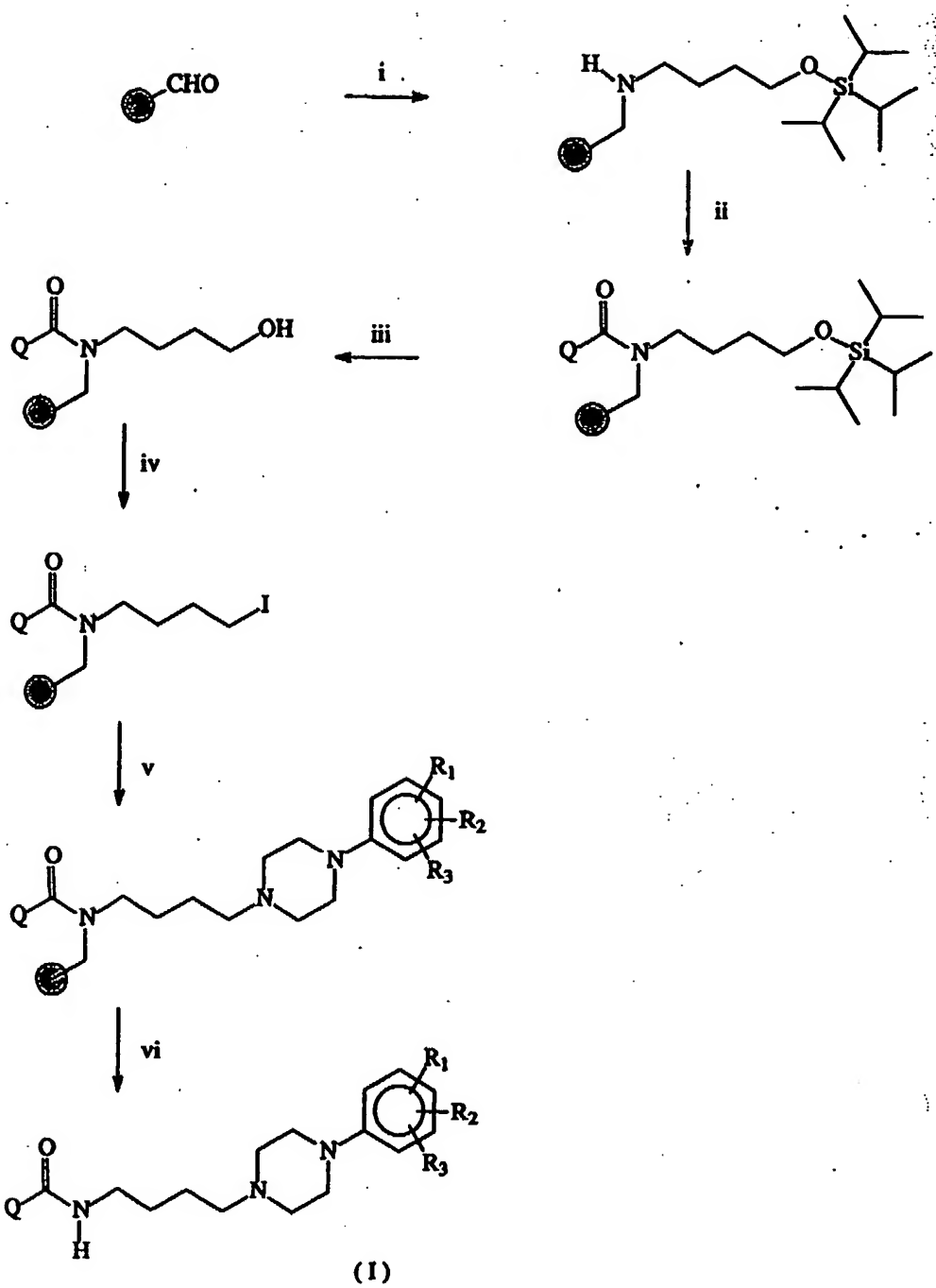
(IV)

wherein R_1, R_2 and R_3 are as described above for the formula (I);

are alkylated with the halogenide derivative obtained in the previous step (v),

acidic cleavage released the products of formula (I) wherein R_1, R_2, R_3 and Q are the same meaning as defined above; from the solid-phase (vi).

This synthetic route is represented by the following Scheme.



(I)

i: "primary amine"/$NaBH(OAc)_3$/AcOH;

ii: "acid"/HBTU/TEA;

iii: Bu_4NF;

iv: I_2/Ph_3P/imidazole;

v: "secondary amine", Hünig-base;

vi: TFA/DCM.

The compounds of formula (I) of the present invention have been found to exhibit high affinity and selectivity for D_3 receptors, and are expected to be useful in the treatment and/or prevention of disease states in which the dopamine D_3 receptors are involved in disease pathology and thus their modulation is required. The compounds of formula (I) have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The compounds of formula (I) may therefore advantageously be used as modulators of D_3 receptors being selective over D_2 receptors.

Dysfunction of the dopaminergic neurotransmitter system is involved in the pathology of several neuropsychiatric disorders, such as schizophrenia, Parkinson's disease and drug abuse. The effect of dopamine is mediated via at least five distinct dopamine receptors belonging to the D_1- (D_1, D_5) or the D_2- (D_2, D_3, D_4) families. D_3 receptors have been shown to have characteristic distribution in the cerebral dopaminergic systems. Namely, high densities were found in certain limbic structures such as nucleus accumbens and islands of Calleja. Therefore, selective targeting of the D_3 receptors may be a promising approach for more selective modulation of dopaminergic functions and consequently for successful therapeutic intervention in several abnormalities such as schizophrenia, emotional or cognitive dysfunctions (Sokoloff, P. et al.: *Nature* **1990**, 347, 146; Schwartz, J.C. et al.: *Clin. Neuropharmacol.* **1993**, 16, 295; Levant, B.: *Pharmacol. Rev.* **1997**, 49, 231), addiction (Pilla, C. et al.: *Nature* **1999**, 400, 371) and Parkinson's disease (Levant, B. et al.: *CNS Drugs* **1999**, 12, 391) or pain (Levant, B. et al.: *Neurosci. Lett.* **2001**, 303, 9). Dopamine D_3 receptors are implicated in regulation of intraocular pressure and agonists at these receptor are capable of decreasing the intraocular pressure (Chu, E. et al: *J. Pharmacol. Exp. Ther.* **2000**, 292, 710), thus D_3 receptor agonists can be useful for the treatment of glaucoma. This invention provides novel compounds of formula (I) which are D_3 dopamine receptor subtype selective ligands. Certain compounds of formula (I) have been found to be dopamine D_3 receptor antagonist, others may be full or partial

agonists. Thus, the invention provides compounds of formula (I) useful in the treatment and/or prevention of neuropsychological disorders including, but not limited to psychoses (e.g. schizophrenia, schizo-affective disorders, etc.), drug (e.g. alcohol, cocaine and nicotine, opioids, etc.) abuse, cognitive impairment accompanying schizophrenia, mild-to-moderate cognitive deficits, amnesia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit/hyperactivity disorder in children, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's disease, neuroleptic induced parkinsonism, tardive dyskinesias) anxiety, sexual disorders, sleep disorders, emesis, aggression, autism, pain, ophthalmological diseases (e.g. glaucoma, etc.).

The invention also provides the use of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or the physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of conditions which require modulation of dopamine D_3 receptors.

A preferred use for D_3 antagonists according to the present invention is in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, depression, anxiety, memory disorders, sexual dysfunction,drug abuse and pain.

A preferred use for D_3 agonists or partial agonists according to the present invention is in the treatment of drug abuse (such as cocaine abuse etc.) and eye diseases (such as glaucoma).

For use in medicine, the compounds of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a new compound of formula (I), and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof and a physiologically acceptable carrier.

The compounds of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention may be administered by any convenient method, for example by oral, parental, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation of the compounds of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention generally consists of a suspension or solution of the compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof in a suitable liquid carrier(s) for example an aqueous solvent, such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the solid form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, cellulose, etc.

A composition in the solid form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention in a steril aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration containing a compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations of the present invention typically comprise a solution or fine suspension of the compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in a single or multidose quantities in steril form is a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosages form can also take the form af a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier, such as sugar and acacia, tragacanth, or gelatine and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional supposiory base, such as cocoa butter.

Compositions for transdermal administration include ointments, gels and patches.

The composition containing a compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof of the present invention is preferably in the unit dose form such as tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1-25 mg) of a compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof calculated as a free base.

The physiologically acceptable compounds of the present invention may normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of formula (I) and/or geometric isomer and/or stereoisomer and/or diastereomer and/or a physiologically acceptable salt and/or hydrate and/or solvate thereof calculated as the free base. The compounds of the present invention can be administered 1 to 4 times per day. The compounds of the present invention will suitably be administered for a period of continous therapy, for example for a week or more.

Biological test methods

Receptor binding assays

1. D_3 receptor binding

Binding study was carried out on rat recombinant D_3 receptors expressed in Sf9 cells using [^{3}H]-spiperone (0.4 nM) as ligand and haloperidol (10 μM) for determination of non-specific binding. The assay was performed according to Research Biochemical International assay protocol for D_3 receptor (Cat. No. D-181).

2. D_2 receptor binding

Binding of [^{3}H]-spiperone (0.5 nM) to rat striatal tissue was measured according to the method of Seeman (*J. Neurochem.* **1984**, 43, 221). The non-specific binding was determined in the presence of (±)-sulpiride (10 μM).

D_3 and D_2 receptor binding data of selected compounds of the invention are listed in the Table hereinbelow.

Compound Code	D_3 IC_{50} (nM)	D_2 IC_{50} (nM)
13190	3.6	169
13191	0.3	72
13426	0.4	425
13852	0.2	240
13857	5.5	613
13963	2.4	1054
14165	0.4	39
70001100	0.5	213
70001493	4.3	417
70001543	0.7	84

One of the most prominent side effects of the first generation antipsychotic compounds, (e.g. chlorpromazine and haloperidol) with preferential blockade at dopamine D_2 and alpha-1 receptors, are the tardive dyskinesia and orthostatic hypotension. The former one is the result of blockade of D_2 receptors in the basal ganglia whereas the latter is the consequence of antagonism of alpha-1 receptors. Compounds in the above table are potent ligands at D_3 receptors (IC-50 values are between 0.2-5.5 nM) and show 47-to 1200-fold selectivity over D_2 receptors. Moreover, the compounds have beneficial profile in terms of potency on D_3 receptors and selectivity towards D_2 receptors than the known D_3 receptor ligands described in the literatute. It is therefore anticipated that no or greatly diminished

adverse effects related to D_2 receptors will occur in the course of therapeutical application of compounds of the present invention.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. These examples illustrate the presently preferred methods for preparing the compounds of the invention.

The structure of all intermediates and end products were elucidated by IR, NMR and MS spectroscopy.

Example 1

4-(Imidazo[2,1-b]thiazol)-6-yl)-benzoic acid

22.4g (0.1 mol) of 4-(2'-bromo-acetyl)-benzonitrile was added to a solution of 10g (0.1 mol) of 2-amino-thiazole in 100ml of acetone, and the mixture was refluxed for 1 hour. The obtained suspension was cooled and stored at 5°C for 16 hours. The intermediate quaternary compound was filtered, and washed with 20ml of diisipropyl-ether. The solid was suspended in 600ml of 5N aqueous hydrochloric acid, and was heated under reflux for 60 hours. The solvent was evaporated in vacuo and the residue was dissolved in 200ml of 2.5N aqueous sodium hydroxide. The solution was decolorized with 5g of carbon and the pH was adjusted to 4.5 with 5N aqueous hydrochloric acid. The suspension was cooled to 10°C and filtered. The solid was washed with ice water (2 x 50 ml) and dried in vacuo at 140°C overnight to give the title compound, 16.7g (72%) melting at 312-315°C.

The following compound was prepared in a similar manner to Example 1:

4-(imidazo[1,2-a]pyrimidin-2-yl)-benzoic acid, m.p.: above 320°C (starting from 2-amino-pyrimidine).

Example 2

1-(4-bromo-2-methoxy-phenyl)-piperazine

To a stirred solution of 11.44g (0.05 mol) of 1-(2-methoxy-phenyl)-piperazine hydrochloride and 8.2g (0.1 mol) of sodium acetate in 150ml of acetic acid 7.99g (0.05 mol) of bromine in 20ml of acetic acid was slowly added in 10-15 min. The temperature was kept at 5-10°C during the addition. After stirring at ambient temperature for 2 hours, the solvent was evaporated in vacuo. To the residue 40ml of water was added, and the pH was adjusted to 11-12 with 20% aqueous sodium hydroxide. The basic mixture was extracted with 3 x 100ml of dichloromethane. The combined organic layer was washed with 100ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 10.2g (75.2%) of the title compound as an oil which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 2:

1-(4-bromo-2-ethoxy-phenyl)-piperazine;
1-(4-bromo-2-methyl-phenyl)-piperazine;
1-(4-bromo-2,3-dimethyl-phenyl)-piperazine;
1-(4-bromo-2-fluoro-phenyl)-piperazine;
1-(4-bromo-3-trifluormethyl-phenyl)-piperazine.

Example 3

4-(4-bromo-2-methoxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester

To a solution of 8.95g (0.033 mol) of 1-(4-bromo-2-methoxy-phenyl)-piperazine in 200ml tetrehydrofuran and 40ml of water 7.64g (0.035 mol) of di-*tert*-butyl dicarbonate was added. The reaction mixture was stirred at ambient temperature overnight and then concentrated in vacuo. The residue was dissolved in 180ml of ethyl acetate, washed with 2 x 40ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by a silica plug (200g) with

hexane/ethyl acetate (4:1) as eluent gave 9.5g (77.5%) of the title compound as a colorless oil which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 3:

4-(4-bromo-2-ethoxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester;
4-(4-bromo-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester;

Example 4

1-(3-methoxy-biphenyl-4-yl)-piperazine

To a stirred solution of 4.06g (10.94 mmol) of 4-(4-bromo-2-methoxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester and 1.61g (13.2 mmol) of phenylboronic acid in the mixed solvent of 75ml of toluene, 55ml of ethanol, and 40ml of 2M aquaeous sodium carbonate 0.63g (5 mol%) tetrakis(triphenylphosphine)palladium(0) was added, under nitrogen. The reaction mixture was vigorously stirred at reflux overnight and then concentrated in vacuo. The residue was dissolved in 100ml of chloroform. The obtained solution was washed with 2 x 100ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by silica gel plug (100g) with chloroform gave an oily residue, which was suspended in 5ml of ethyl acetate, 80ml of 2.5N hydrochloric acid in ethyl acetate was added, and the mixture was stirred at 0-5°C for 4 hours. The solid was filtered and dissolved in 40ml of water. The pH was adjusted to 11-12 with 1N aquaeous sodium hydroxide. The basic mixture was extracted with 3 x 50ml of dichloromethane. The combined organic layer was washed with 50ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 1.5g (51.1%) of the title compound as a white solid which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 4:

1-(3-ethoxy-biphenyl-4-yl)-piperazine;

1-(3-fluoro-biphenyl-4-yl)-piperazine;
1-(3,2'-dimethoxy-biphenyl-4-yl)-piperazine.

Example 5

4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyronitrile

To 300ml of acetonitrile 21.4g (0.08 mol) of 1-(2,3-dichloro-phenyl)-piperazine hydrochloride, 8.7g (0.084 mol) of 4-chlorobutyronitrile, 27.6g (0.2 mol) of potassium carbonate and a catalytic amount of sodium iodide were added, and the mixture was stirred at reflux for 10 hours. The solid was filtered, and the filtrate was concentrated in vacuo. Purification by silica gel plug (200g) with ethyl acetate gave 19.6g (82.2%) of the title compound as a solid which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 5:

4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyronitrile;
4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-butyronitrile;
4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyronitrile;
4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butyronitrile;
4-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyronitrile;
4-[4-(3-ethoxy-biphenyl-4-yl)-piperazin-1-yl]-butyronitrile;
4-[4-(3-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butyronitrile;
4-[4-(3,2'-dimethoxy-biphenyl-4-yl)-piperazin-1-yl]-butyronitrile.

Example 6

4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butylamine

To a vigorously stirred solution of 12.3g (41.25 mmol) of 4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyronitrile in 350ml of ethanol and 140ml of 2.5N aquaeous sodium hydroxide 17.7g of aluminium-nickel alloy (assay of nickel: 50%) was added in portions. The temperature was kept at 5-10°C during the addition.

The mixture was stirred at ambient temperature overnight. The solid was filtered, and the organic solvent was evaporated in vacuo. The aquaeous residue was extracted with 3 x 100ml of chloroform. The combined organic layer was washed with 200ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 11.5g (82.3%) of the title compound which was used in the next step without further purification. Assay with acidimetric titration (HCl): 89.2%

The following compounds were prepared in a similar manner to Example 6:

4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butylamine;
4-[4-(3-ethoxy-biphenyl-4-yl)-piperazin-1-yl]-butylamine;
4-[4-(3-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butylamine;
4-[4-(3,2'-dimethoxy-biphenyl-4-yl)-piperazin-1-yl]-butylamine.

Example 7

2-{4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione

To 200ml of acetonitrile 7.43g (27.4 mmol) of 1-(4-bromo-2-methoxy-phenyl)-piperazine, 7.73g (27.4 mmol) of N-(4-bromobutyl)-phthalimide, 9.45g (68.5 mmol) of potassium carbonate and a catalytic amount of sodium iodide were added, and the mixture was stirred at reflux for 10 hours. The solid was filtered, and the filtrate was concentrated in vacuo. The residue was triturated with 100ml of diethyl ether. The obtained solid was filtered, washed with 50ml of diethyl ether, and dried to give 11.2g (86.5%) of the title compound which was used in the next step without further purification.

The following compounds were prepared in a similar manner to Example 7:

2-{4-[4-(4-bromo-2-ethoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(4-bromo-2-methyl-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(4-bromo-2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(4-bromo-2-fluoro-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(4-bromo-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(5-cyano-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione;
2-{4-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione.

Example 8

4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butylamine

To a suspension of 11.1g (23.5 mmol) of 2-{4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione in 250ml of ethanol 2.28ml (47 mmol) of hydrazine monohydrate was added, and the mixture was stirred at ambient temperature for 12 hours, and then at reflux temperature for two hours. The volume was concentrated to 60-80ml in vacuo, then 250ml of water was added. The pH was adjusted to 1-2 with 1N aquaeous hydrochloric acid. The precipitated solid was filtered, and the pH of the filtrate was adjusted to 10 with aquaeous ammonia solution (assay of ammonia: 25%). The basic mixture was extracted with 3 x 100ml of chloroform. The combined organic layer was washed with 2 x 100ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 7.8g (83.6%) of the title compound which was used in the next step without further purification. Assay with acidimetric titration (HCl): 86.2%

The following compounds were prepared in a similar manner to Example 8:

4-[4-(4-bromo-2-ethoxy-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(4-bromo-2-methyl-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(4-bromo-2,3-dimethyl-phenyl)-piperazin-1-yl]-butylamine;

4-[4-(4-bromo-2-fluoro-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(4-bromo-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(5-cyano-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butylamine;
4-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-butylamine.

Example 9

N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-quinoline-3-carboxamide (70001610)

To a solution of 0.14g (0.8 mmol) of quinoline-3-carboxylic acid in 15ml of dimethylformamide 0.12g (0.8 mmol) of 1-hydroxybenzotriazole hydrate and 0.165g (0.8 mmol) of 1,3-dicyclohexylcarbodiimide were added. The mixture was stirred at ambient temperature for 10 minutes. To the obtained solution 0.287g (0.8 mmol) of 4-[4-(5-cyano-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine (assay of amine: 91.1%) in 5ml dimethylformamide was added, and the reaction mixture was stirred at ambient temperature overnight. The solvent was concentrated in vacuo. Purification by column chromatography on silica gel (30g) with chloroform/ethanol (15:1) as eluent followed by crystallization from ethyl ether gave 0.28g (72.7%) of the title compound, melting point 153-155°C.

The following compounds were prepared in a similar manner to Example 9:

N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-quinoline-4-carboxamide, m.p.: 141°C (70001480);
4-bromo-N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-benzamide, m.p.: 137°C (70001493);
N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 186-187°C (70001748);
3-bromo-N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-benzamide, m.p.: 112°C (70001767).

Example 10

N-[4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl]-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide (13191)

To a cooled (0°C) solution of 1.05g (4.3 mmol) of 4-(imidazo[2,1-b]thiazol-6-yl)-benzoic acid in 30ml of dimethylformamide 0.47ml (4.3 mmol) of 4-methylmorpholine and 0.53ml (4.3 mmol) of isobutyl chloroformate were added. The reaction mixture was stirred at 0°C for 10 minutes. To the obtained solution 1.37g (4.3 mmol) of 4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butylamine (assay of amine: 94.6%) in 20ml of dimethylformamide was added, and the reaction mixture was stirred at ambient temperature overnight. The solvent was concentrated in vacuo. Purification by column chromatography on silica gel (150g) with chloroform/methanol (9:1) as eluent followed by crystallization from ethyl ether gave 0.95g (41.8%) of the title compound, melting point 219-222°C.

The following compounds were prepared in a similar manner to Example 10:

N-[4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl]-9H-β-carboline-3-carboxamide, m.p.: 204-206°C (13190);
N-[4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl]-4-(4-fluoro-phenyl)-1H-pyrrole-3-carboxamide, m.p.: 245-247°C (13255);
N-[4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl]-9H-β-carboline-3-carboxamide, m.p.: 230°C (13374);
N-[4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl]-9H-β-carboline-3-carboxamide, m.p.: 198-199°C (13425);
N-[4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl]-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:205-207°C (13426);
N-[4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl]-4-(imidazo[1,2-a]pyridin-2-yl)-benzamide, m.p.: 226°C (13671);
N-[4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl]-4-(imidazo[1,2-a]pyrimidin-2-yl)-benzamide, m.p.: 208°C (13704);

N-{4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl}-2,3-dichloro-benzamide, m.p.: 148°C (13837);
N-{4-[4-(4-bromo-2-methyl-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:209°C (13857);
N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(pyrimidin-4-yl)-benzamide, m.p.: 185-186°C (13886);
N-{4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:199°C (13894);
N-{4-[4-(3-ethoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:178°C (13911);
N-{4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:200°C (13913);
N-{4-[4-(4-bromo-2-ethoxy-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:202°C (13928);
N-{4-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:222-223°C (13960);
N-{4-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-4-(imidazo[1,2-a]pyridin-2-yl)-benzamide, m.p.: 224°C (13963);
N-{4-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-quinoline-3-carboxamide, m.p.:160°C (14103);
N-{4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:206-207°C (14144);
N-{4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[1,2-a]pyrimidin-2-yl)-benzamide, m.p.: 263°C (14145);
N-{4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[1,2-a]pyridin-2-yl)-benzamide, m.p.: 235°C (14146);
N-{4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(pyrimidin-4-yl)-benzamide, m.p.: 175°C (14165);
N-{4-[4-(4-bromo-2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:232-233°C (14212);
N-{4-[4-(4-bromo-2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-quinoline-3-carboxamide, m.p.:165°C (14214);

N-{4-[4-(4-bromo-2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 197-199°C (14215);

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 182-183°C (14231);

N-{4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 164-165°C (14232);

N-{4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[1,2-a]pyridin-2-yl)-benzamide, m.p.: 182-185°C (14233);

N-{4-[4-(2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4'-hydroxy-biphenyl-4-carboxamide, m.p.: 158-159°C (14234);

N-{4-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-(imidazo[2,1-b]thiazol-6-yl)-benzamide, m.p.:233°C (14304);

N-{4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butyl}-4'-hydroxy-biphenyl-4-carboxamide, m.p.: 186-187°C (70001252);

N-{4-[4-(3-fluoro-biphenyl-4-yl)-piperazin-1-yl]-butyl}-4-methyl-benzamide, m.p.: 194-196°C (70001288);

N-{4-[4-(4-bromo-2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4-bromo-benzamide, m.p.: 170-171°C (70001339);

N-{4-[4-(4-bromo-2-fluoro-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 209-210°C (70001340);

N-{4-[4-(3,2'-dimethoxy-biphenyl-4-yl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide, m.p.: 147-148°C (70001415);

N-{4-[4-(4-bromo-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-methoxy-benzamide,.m.p.: 150-151°C (70001593);

N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-dimethylamino-benzamide, m.p.: 164-165°C (70001718);

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-dimethylamino-benzamide, m.p.: 170-171°C (70001821);

N-{4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-bromo-benzamide, m.p.: 157-158°C (70001848);

Example 11

N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-4-cyano-benzamide (70002107)

To a cooled (0-5°C) solution of 1.6g (5 mmol) of 4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butylamine (assay of amine: 94.6%) and 1ml (7.2 mmol) of triethylamine in 50ml of 1,2-dichloroethane 0.83g (5 mmol) of 4-cyanobenzoyl chloride in 10ml of 1,2-dichloroethane was added slowly. The reaction mixture was stirred at ambient temperature for 2 hours. The obtained solution was washed with 20ml of 5% aquaeous sodium carbonate, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by column chromatography on silica gel (100g) with chloroform/ethanol (9:1) as eluent followed by crystallization from ethanol gave 0.8g (37.1%) of the title compound, melting point 174-178°C.

The following compound was prepared in a similar manner to Example 11:

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-cyano-benzamide, m.p.: 143-144°C

(70001899).

Example 12

N-{4-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-3-(pyridin-3-yl)-acrylamide (70001808)

To a solution of 0.15g (1 mmol) *trans*-3-(3-pyridyl)acrylic acid in 15ml of dimethylformamide 0.155g (1 mmol) of 1-hydroxybenzotriazole hydrate and 0.2g (1 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride were added. The mixture was stirred at ambient temperature for 10 minutes. To the obtained solution 0.33g (1 mmol) of 4-[4-(5-cyano-3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine (assay of amine: 91.1%) in 5ml of dimethylformamide was added, and the reaction mixture was stirred at ambient temperature overnight. The solvent was concentrated in vacuo. Purification by column chromatography on

silica gel (30g) with chloroform/methanol (4:1) as eluent followed by crystallization from ethyl ether gave 0.28g (61.2%) of the title compound, melting point 158°C.

The following compounds were prepared in a similar manner to Example 12:

N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-1H-indole-5-carboxamide, m.p.: 255°C (14306);

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-1H-indole-5-carboxamide, m.p.: 138°C (70001100);

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-3-(1H-indole-3-yl)-acrylamide, m.p.: 126°C (70001543);

N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-3-(1H-indole-3-yl)-acrylamide, m.p.: 138°C (70001543).

Example 13

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-(1-allyl-1H-imidazol-4-yl)-benzamide (13852)

To a stirred solution of 1.079g (4 mmol) of 4-(1-allyl-1H-imidazol-4-yl)-benzoic acid hydrochloride in 100ml of dimethylformamide 0.66ml (6 mmol) of 4-methylmorpholine and 1.517ml (4 mmol) of O-benzotriazol-N,N,N',N'-tetramethyluronium hexafluorophosphate were added. The reaction mixture was stirred at ambient temperature for 20 minutes. To the obtained solution 1.3g (4 mmol) of 4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butylamine (assay of amine: 92%) in 20ml of dimethylformamide was added, and the reaction mixture was stirred at ambient temperature overnight. The solvent was concentrated in vacuo. Purification by column chromatography on silica gel (150g) with chloroform/methanol (9:1) as eluent followed by crystallization from ethyl ether gave 0.55g (26.9%) of the title compound, melting point 157-159°C.

The following compounds were prepared in a similar manner to Example 13:

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-(1-methyl-1H-imidazol-4-yl)-benzamide, m.p.: 187-188°C (13784);
N-{4-[4-(4-bromo-2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4-(1-methyl-1H-imidazol-4-yl)-benzamide, m.p.: 207-209°C (13834).

Example 14

N-{4-[4-(3-aminocarbonyl-phenyl)-piperazin-1-yl]-butyl}-4-bromo-benzamide (70001993)

To a solution of 0.11 g (0.25 mmol) of N-{4-[4-(3-cyano-phenyl)-piperazin-1-yl]-butyl}-4-bromo-benzamide in 2 ml of dimethylsulfoxide 20mg of potassium carbonate and 0.15ml of 30% H_2O_2 were added. The reaction mixture was stirred at ambient temperature for 2 hours. 20ml of water was added to the mixture, the precipitate filtered, and washed with water. Crystallization from methanol gave 0.05g (43.5%) of the title compound, melting point: 193°C.

Example 15

4-Triisopropylsilanyloxy-butylamine

To an ice-cooled solution of 10g (0.11 mol) of 4-aminobutanol and 16.5ml (0.12 mol) of triethylamine in 100ml of dichloromethane 24ml (0.12 mol) of chlorotriisopropylsilane in 50ml of dichloromethane was added. The mixture was stirred at ambient temperature for 20 hours. The obtained suspension was extracted with 300ml of water. The aquaeous phase was further extracted with 3 x 50ml of dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated in vacuo to give 26.5g (96%) of the title compound which was used in the next step without further purification.

Example 16

Polymer-bound triisopropylsilanyloxy-butylamine

To a slowly stirred suspension of 10g (16 mmol) of 4-formyl-3-methoxy-phenoxy polystyrene in 400ml of dichloromethane 17.2g (70 mmol) of 4-triisopropylsilanyloxy-butylamine, 12.6ml glacial acetic acid, and 15g (70 mmol) of sodium triacetoxyborohydride were added in small portion within 30 minutes. After 3 hours another 6g (28.5 mmol) of sodium triacetoxyborohydride was added to the suspension. The stirring was continued at ambient temperature for 16 hours. The resin was filtered, and washed twice with 400-400ml of the following solvents in sequence: dichloromethane, methanol, 10 % triethylamine in dimethylformamide, methanol, dimethylformamide, tetrahydrofuran. The resin was dried in vacuo to give 12.9g of the title material.

Example 17

Polymer-bound N-(4-triisopropylsilanyloxy-butyl)-3-methyl-benzamide

To 0.12g (0.14 mmol) of polymer-bound triisopropylsilanyloxy-butylamin 1.26ml (0.63 mmol) of 0.5M 3-methyl-benzoic acid in dimethylformamide, 0.24ml (0.42 mmol) of 25% triethylamine in dimethylformamide, 1.26ml (0.63 mmol) of 0.5M O-benzotriazol-N,N,N',N'-tetramethyluronium hexafluorophosphate in dimethylformamide were added, and the reaction mixture was shaken on an orbital shaker with 100/min rotation at ambient temperature for 5 hours. The resin was filtered, washed in sequence with 2x4ml of dimethylformamide, 2 x 4ml of methanol, 2 x 4ml of tetrahyrofuran, 2 x 4ml of methanol and 2 x 4 ml of tetrahydrofuran.

Example 18

Polymer-bound N-(4-hydroxybutyl)-3-methyl-benzamide

To the polymer-bound N-(4-triisopropylsilanyloxy-butyl)-3-methyl-benzamide obtained in the previous step 0.11g (0.42 mmol) of

tetrabutylammonium fluoride hydrate in 2ml of tetrahydrofuran was added. The reaction mixture was shaken on an orbital shaker with 100/min rotation at ambient temperature for 1 hour. The resin was filtered and 0.11g (0.42 mmol) of tetrabutylammonium fluoride hydrate in 2ml of tetrahydrofuran was added to it again. The reaction mixture was shaken on an orbital shaker with 100/min rotation at ambient temperature for 1 hour. The resin was filtered, washed in sequence with 2 x 4ml of tetrahydrofuran, 2 x 4ml of methanol, 2 x 4ml of dichloromethane, 2 x 4ml of methanol, 2 x 4 ml of tetrahydrofuran, 2 x 4ml of methanol and 2 x 4ml of dichloromethane.

Example 19

Polymer-bound N-(4-iodobutyl)-3-methyl-benzamide

To the polymer-bound N-(4-hydroxybutyl)-3-methyl-benzamide obtained in the previous step 0.0378g (0.56 mmol) of imidazole in 0.56ml of dichloromethane was added. After 5 min shaking 0.289g (0.56 mmol) of diiodotriphenylphosphorane in 3.73ml of dichloromethane was added to the mixture. The reaction mixture was shaken on an orbital shaker with 100/min rotation at ambient temperature for 7 hours. The resin was filtered washed in sequence with 3 x 4ml of dichloromethane, 2 x 4ml of methanol, 2 x 4ml of dichloromethane and 3 x 6ml of dimethylformamide.

Example 20

Polymer-bound N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-3-methyl-benzamide

To the polymer-bound N-(4-iodobutyl)-3-methyl-benzamide obtained in the previous step 0.144g (0.48 mmol) of 1-(3-trifluormethyl-phenyl)-piperazine in 0.48ml of dimethylformamide was added. The mixture was shaken on an orbital shaker with 100/min rotation for 5 min, then 0.29ml (0.48 mmol) of 25% diisopropylethylamine in dimethylformamide was added to it. The reaction mixture was shaken on an orbital shaker with 100/min rotation at 95 ^{0}C for 3 hours. The

resin was filtered, washed in sequence with 2 x 4ml of dimethylformamide, 2 x 4ml of methanol, 2 x 4ml of dichloromethane, 2 x 4ml of dimethylformamide and 3 x 2ml of dichloromethane.

Example 21

N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-3-methyl-benzamide (80000180)

To the polymer-bound N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-3-methyl-benzamide obtained in the previous step 2ml of trifluoroacetic acid/dichloromethane (1:2) was added and the mixture was shaken on an orbital shaker with 100/min rotation for 2 hours. The resin was filtered, and washed twice with 2ml of dichloromethane. The combined filtrate was concentrated in vacuo to give the title compound.

Molecular weight (calculated): 419.49;

Molecular weight (found): 419.491;

k': 3.567.

The LC/MS analysis was performed using an HP1100 binary gradient system, controlled by ChemStation software. HP diode array detector was used to acquire UV spectra at λ = 240nm. Analytical chromatographic experiments were made on Discovery C_{16}-Amide, 5cm X 4.6mm X 5µm column with a flow rate of 1ml/min for qualification (purity, capacity factor). All experiments were performed using HP MSD single quadruple mass spectrometer equipped with an electrospray ionisation source to determine the structure.

$k' = t_R - t_0 / t_0$

wherein

k'= capacity factor

t_R = retention time

E.g. the following compounds were prepared in a similar manner to Example 21:

N-{4-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-butyl}-4-fluoro-benzamide,
MW (calc.): 383.51, MW (found): 383.5000, k':3.525 (80000040);
N-{4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-butyl}-4-methylsulfanyl-benzamide,
MW (calc.): 451.55, MW (found): 451.551, k':3.613 (80000182);
N-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butyl}-3,4-diethoxy-benzamide,
MW (calc.): 494.46, MW (found): 494.463, k':3.635 (80000330).

Example 22

Pharmaceutical formulation

a) Intravenous injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

b) Bolus injenction

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-solvent	to 5 ml

Buffer: suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent: typically water but may also include cyclodextrins (1-100 mg) and co-solvents, such as propylene glycol, polyethylene glycol and alcohol.

c) Tablet

Compound of formula (I)	1-40 mg
Diluent/Filter(may also include cyclodextrins)	50-250mg
Binder	5-25 mg
Disintegrant (may also include cyclodextrins)	5-50 mg

Lubricant	1-5 mg
Cyclodextrin	1-100 mg

Diluent: e.g. mycrocrystalline cellulose, lactose starch.

Binder: e.g. polyvinylpyrrolidone, hydroxypropylmethylcellulose.

Disintegrant: e.g. sodium starch glycolate, crospovidone.

Lubricant: e.g. magnesium stearate, sodium stearyl fumarate

d) Oral suspension

Compound of formula (I)	1-40 mg
Suspending agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg

Suspending agent: e.g. xanthan gum, mycrocrystalline cellulose.

Diluent: e.g. sorbitol solution, tipically water.

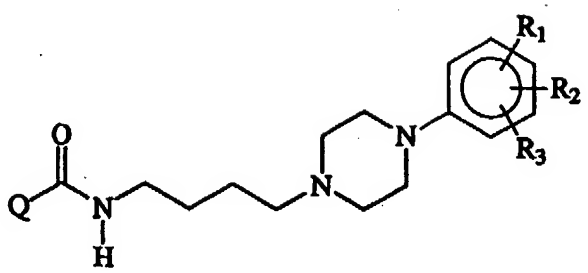
Preservative: e.g. sodium benzoate.

Buffer: e.g. citrate.

Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin.

What we claim:

1. A compound of formula (I):



(I)

wherein

R_1, R_2 and R_3 are the same or different and represent hydrogen, halogen, C_{1-6} alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6} alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl; hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group,

excluding when

a) $R_1 = R_2 = R_3 = H$;

b) $R_1 = R_2 = H$ and

$R_3 = C_{1-6}$ alkoxy in the position 2 or R_3 is in the position 4 of the piperazinyphenyl moiety;

c) $R_1 = H$ and

$R_2 = R_3 = C_{1-6}$ alkoxy; and

Q represents an optionally substituted C_{1-6}alkyl, C_{1-6}alkenyl, phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl,

pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 2,3-dihydro-3-oxo-4H-benoxazinyl, 1,2-dihydro-2-oxo-3H-indolyl or β-carbolinyl substituted by one or more substituent(s) independently selected from hydrogen, halogen, hydroxy, cyano, amino, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, methylenedioxy, C_{1-6}alkylamino, C_{1-6}alkanoylamino, C_{1-6}alkylthio, optionally substituted aroyl, aryloxy, aminosulfonyl, arylsulfonylamido, optionally substituted mono or bicyclic aromatic or heteroaromatic ring

excluded when

Q = phenyl with one fluorine or chlorine substituent in any position,

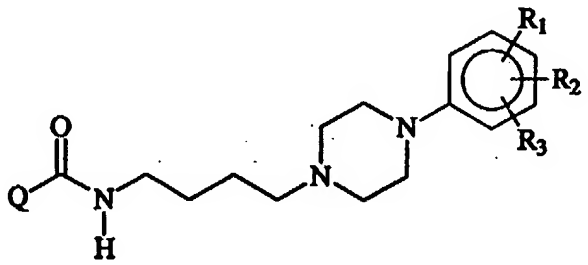
$R_1 = R_2 = H$ and

R_3 = trifluoromethyl in the position 3 of the piperazinyphenyl moiety,

simultaneously;

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

2. A compound of formula (I):



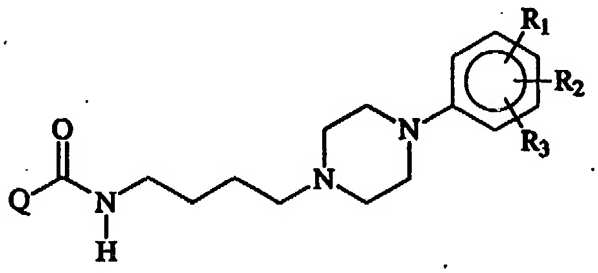
wherein

R_1, R_2 and R_3 are the same or different and represent halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, hydroxy, trifluoromethyl, (un)substituted amino, aminocarbonyl or (un)substituted phenyl or naphthyl groups in the 2,3,4 positions of the piperazinyphenyl moiety, two adjacent groups of R_1, R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group; and

Q represents an optionally substituted thienyl, pyridyl, pyrimidyl, pyrazinyl, quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl, indolyl, β-carbolinyl; C_{1-6}alkyl substituted by an (un)substituted aryl or heteroaryl group; C_{1-6}

alkenyl substituted by an (un)substituted aryl or heteroaryl group; phenyl substituted by bromine, C_{1-6}(di)alkylamino, C_{1-6}alkyl, C_{1-6}alkoxy or (un)substituted aryl or heteroaryl group(s);
and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

3. A compound of formula (I):



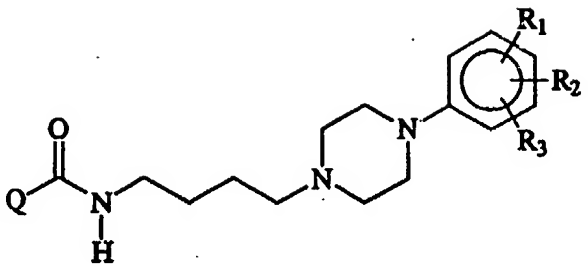
wherein

R_1 = H;

R_2 and R_3 are the same or different and represent halogen, C_{1-6} alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, (un)substituted C_{1-6}alkanoyloxy , (un)substituted amino, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, (un)substituted phenyl or naphthyl, (un)substituted mono or bicyclic heterocyclic groups in the 2,3-, 2,4- or 3,5 positions of the piperazinyphenyl moiety, two adjacent groups of R_2 and R_3 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group; and

Q represents an optionally substituted thienyl, pyridyl, pyrimidyl, pyrazinyl, quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl, indolyl, β-carbolinyl; C_{1-6}alkyl substituted by an (un)substituted aryl or heteroaryl group; C_{1-6}alkenyl substituted by an (un)substituted aryl or heteroaryl group; phenyl substituted by bromine, C_{1-6}(di)alkylamino, C_{1-6}alkyl, C_{1-6}alkoxy or (un)substituted aryl or heteroaryl group(s);
and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

4. A compound of formula (I):



(I)

wherein

$R_1 = R_2 = H$;

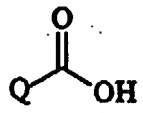
R_3 represents halogen, C_{1-6}alkyl, cyano, hydroxy, trifluoromethyl, C_{1-6} alkylsulfonyloxy, trifluoromethanesulfonyloxy, (un)substituted C_{1-6}alkanoyloxy, (un)substituted amino, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl, hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, (un)substituted phenyl or naphthyl, (un)substituted mono or bicyclic heterocyclic group in the 2 or 3 position of the piperazinyphenyl moiety; and

Q represents an optionally substituted thienyl, pyridyl, pyrimidyl, pyrazinyl, quinolinyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzimidazolyl, indolyl, β-carbolinyl; C_{1-6}alkyl substituted by an (un)substituted aryl or heteroaryl group; C_{1-6} alkenyl substituted by an (un)substituted aryl or heteroaryl group; phenyl substituted by bromine, C_{1-6}(di)alkylamino, C_{1-6}alkyl, C_{1-6}alkoxy or (un)substituted aryl or heteroaryl group(s);

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

5. A process for preparing compounds of formula (I) as claimed in any of claims 1 to 4 and and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof which comprises

a) reacting a compound of formula (II):



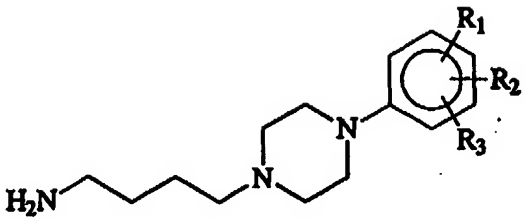
(II)

wherein

Q is as defined in any of claims 1 to 4;

or derivatives thereof

with an amine of formula (III):



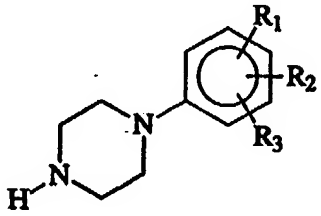
(III)

wherein

R_1, R_2 and R_3 are as defined in any of claims 1 to 4;

or derivatives thereof; or

b) reacting a compound of formula (IV):



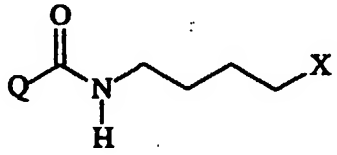
(IV)

wherein

R_1, R_2 and R_3 are as defined in any of claims 1 to 4;

or derivatives thereof

with a compound of formula (V):



(V)

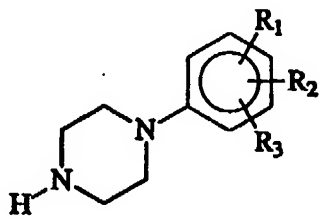
wherein

Q is as defined in any of claims 1 to 4; and

X is a leaving group, preferably chlorine, bromine, iodine, tosylate or mesylate;

or derivatives thereof; or

c) reacting a compound of formula (IV):



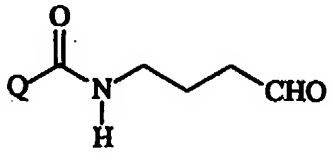
(IV)

wherein

R_1, R_2 and R_3 are as defined in any of claims 1 to 4;

or derivatives thereof

with a compound of formula (VI):



(VI)

wherein

Q is as defined in any of claims 1 to 4;

or derivatives thereof; and

if desired

interconverting one compound of formula (I), wherein R_1, R_2, R_3 and Q are as defined in any of claims 1 to 4 to a different compound of formula (I) wherein R_1, R_2, R_3 and Q are as defined in any of claims 1 to 4; and/or

where appropriate, separating the *cis*- and/or *trans*- isomers and/or enantiomers and/or diastereomers of compounds of formula (I), or intermediates thereto, wherein R_1, R_2, R_3 and Q are as defined in any of claims 1 to 4, by conventional methods;

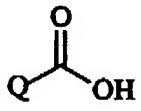
and thereafter optionally forming salts and/or hydrates and/or solvates of formula (I), wherein R_1, R_2, R_3 and Q are as defined in any of claims 1 to 4.

6. A process for preparing a compound of formula (I) as defined in any of claims 1 to 4 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof which comprises:preparing a compound of formula (I) on solid support.

7. A process according to claim 6 which comprises:

(i) attaching a protected 4-aminobutanol derivative to a polystyrene resin by reductive amination;

(ii) acylating the amino group of the compounds obtained with carboxylic acid of formula (II):



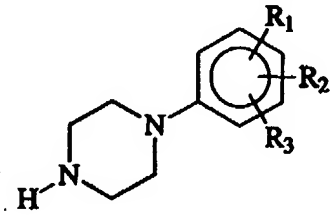
(II)

wherein Q is as defined in claim 6;
or derivatives thereof;

(iii) removing the O-protective group from the compound obtained;

(iv) converting the terminal free hydroxyl group into halogenide with a halogenation agent;

(v) alkylating the amine derivatives of formula (IV):



(IV)

wherein R_1, R_2 and R_3 are as defined in claim 6;
with the halogenide derivative obtained in the previous step;

(vi) releasing compounds of formula (I) wherein R_1, R_2 and R_3 are as defined in claim 6; from the solid support by cleavage; and

if desired

interconverting one compound of formula (I) wherein Q, R_1, R_2 and R_3 are as defined in claim 6 to a different compound of formula (I) wherein Q, R_1, R_2 and R_3 are as defined in claim 6;

where appropriate, separating the enantiomers and/or diastereomers and/or *cis*- and/or *trans*- isomers of compounds of formula (I), or intermediates thereto, wherein Q, R_1, R_2 and Y are as defined in claim 5; by conventional methods;

and optionally thereafter forming a salt and/or hydrate and/or solvate of formula (I) wherein Q, R_1, R_2 and R_3 are as defined in claim 6.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 4 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and physiologically acceptable carriers therefore.

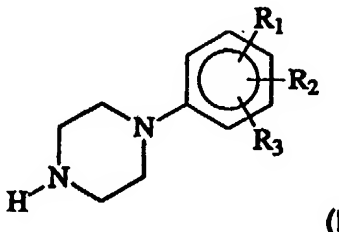
9. The use of a compound of formula (I) as claimed in any of claims 1 to 4 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of dopamine receptors.

10. The use according to claim 9 wherein the dopamine receptors are dopamine D_3 receptors.

11. A method of treating and/or preventing a condition which requires modulation of dopamine receptors which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in any of claims 1 to 4 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof.

12. A method according to claim 11 wherein the dopamine receptors are dopamine D_3 receptors.

13. A compound of formula (IV):



(IV)

wherein

R_1 and R_2 are the same or different and represent hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, hydroxy, trifluoromethyl, C_{1-6}alkylsulfonyloxy, trifluoromethanesulfonyloxy, optionally substituted C_{1-6}alkanoyloxy, amino, aminoalkyl, carboxy, aminocarbonyl, N-hydroxycarbamimidoyl, carbamimidoyl; hydroxycarbamoyl, thiocarbamoyl, sulfamoyl, optionally substituted phenyl or naphthyl, optionally substituted mono or bicyclic heterocyclic group, two adjacent groups of R_1 and R_2 may combine to form an optionally substituted fused mono or bicyclic heterocyclic group; and

R_3 is optionally substituted phenyl,

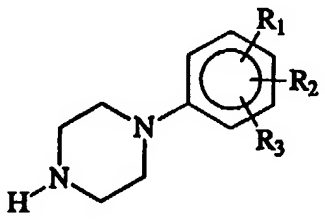
excluding when

$R_1 = R_2 = H$;

and/or salts and/or hydrates and/or solvates thereof.

14. A process for preparing piperazine derivatives of formula (IV) as defined in claim 13 and/or salts and/or hydrates and/or solvates thereof which comprises

I) protecting the secondary amine of a piperazin derivative of formula (IV):



(IV)

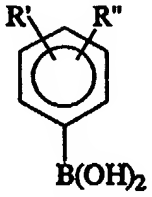
wherein

R_1 and R_2 are as defined in claim 12, and

R_3 is halogen; or

derivatives thereof;

ii) reacting the compound obtained with a compound of formula (VII):



(VII)

wherein

R' and R" are the same or different and represent hydrogen, halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyloxy, amino or alkyl amino;

in the presence of a catalyst applied usually in Suzuki coupling and a base, or derivatives thereof; and

iii) deprotecting the piperazine derivative obtained;

iv) optionally forming salts and/or hydrates and/or solvates of formula (IV) wherein R_1, R_2 and R_3 are as defined in claim 13.

15. The use of a piperazine derivative of formula (IV) as claimed in claim 13 or salts and/or hydrates and/or solvates thereof as key intermediate in the manufacture of acid amide derivatives of formula (I) having selective dopamine D_3 receptor activity.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/HU 02/00095

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61K31/495 A61K31/542 A61K31/519 A61K31/506
C07D215/54 C07D295/12 C07D213/56 C07D513/04 C07D471/04
C07D487/04 C07D207/34 C07D239/26 C07D209/42 C07D233/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOYFIELD I ET AL: "N-(substituted-phenyl) piperazines: antagonists with high binding and functional selectivity for dopamine D4 receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 11, 4 June 1996 (1996-06-04), pages 1227-1232, XP004134859 ISSN: 0960-894X table 1, compounds 2,3,10	1,9,13
Y	the whole document	10
X	DE 197 56 236 A (KLINGE CO CHEM PHARM FAB) 1 July 1999 (1999-07-01) examples 64,68-72,74-76,83,95,96 claim 1	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2002	27/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/HU 02/00095

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 C07D215/50 C07D209/18 C07D295/06 C07D295/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 210 782 A (DAINIPPON PHARMACEUTICAL CO) 4 February 1987 (1987-02-04) table 5 claim 1	1
X	WO 93 21179 A (ASTRA AB) 28 October 1993 (1993-10-28) claims 1,2	1
X,P	WO 02 055496 A (BOMBRUN AGNES ;BOUILLOT ANNE MARIE JEANNE (FR); DUMAITRE BERNARD A) 18 July 2002 (2002-07-18) example 22 claim 13	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00095

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 03833 A (SUGIMOTO MASAHIKO ;NARUTO SHUNJI (JP); SANKYO CO (JP); IWATA NOBUY) 28 January 1999 (1999-01-28) examples (pages 28-85); claim 1	1
X	FR 2 261 756 A (ROUSSEL UCLAF) 19 September 1975 (1975-09-19) claim 1	1
X	EP 0 434 561 A (ADIR) 26 June 1991 (1991-06-26) example 9 claim 1	1
Y	WO 97 34889 A (CHEN XI ;NEUROGEN CORP (US); YUAN JUN (US)) 25 September 1997 (1997-09-25) page 3, line 1 - line 19 claims 1,6-12,14-16	1,9,10
Y	MURRAY P J ET AL: "A novel series of arylpiperazines with high affinity and selectivity for the dopamine D3 receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 5, no. 3, 2 February 1995 (1995-02-02), pages 219-222, XP004135762 ISSN: 0960-894X the whole document	1,9,10
X	scheme 2	13
Y	WO 99 02503 A (LE BRIS THEOPHILE MARIE ;NEUMANN SCHULTZ BARBARA (DE); BASF AG (DE) 21 January 1999 (1999-01-21) page 2, line 6 - line 10 claim 1	1,9,10
Y	US 5 872 119 A (SCHWARTZ JEAN-CHARLES ET AL) 16 February 1999 (1999-02-16) examples 1,4 claims 1,4	1,9,10
X	column 4, line 1 - line 10 example 1B	13
Y	WO 97 38989 A (CHEN XI ;NEUROGEN CORP (US); WASLEY JAN W F (US)) 23 October 1997 (1997-10-23) table 1 example 2 claim 11	1,9,10
X	example 1	13

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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/HU 02/00095

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 38990 A (CHEN XI ;NEUROGEN CORP (US); YUAN JUN (US)) 23 October 1997 (1997-10-23) examples 2,3 claim 9	1,9,10
X	example 1	13
Y	WO 97 10229 A (CHEN XI ;NEUROGEN CORP (US); YUAN JUN (US)) 20 March 1997 (1997-03-20) claims 1-21,24,25	1,9,10
Y	WO 96 02246 A (BASF AG ;HELLENDAHL BEATE (DE); LANSKY ANNEGRET (DE); RENDENBACH M) 1 February 1996 (1996-02-01) claim 1	1,9,10
Y	WO 96 02249 A (RENDENBACH MUELLER BEATRICE ;BACH ALFRED (DE); BASF AG (DE); UNGER) 1 February 1996 (1996-02-01) claim 1	1,9,10
Y	WO 00 67847 A (BASF AG ;GROSS GERHARD (DE); STARCK DOROTHEA (DE); MUEHLBAUER BERN) 16 November 2000 (2000-11-16) claim 1	1,9,10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 11, 12

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

national application No.
PCT/HU 02/00095

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11, 12
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19756236 A	01-07-1999	DE 19756236 A1	01-07-1999
		AU 2054399 A	05-07-1999
		WO 9931063 A1	24-06-1999
		EP 1060163 A1	20-12-2000
		JP 2002508356 T	19-03-2002
		ZA 9811235 A	08-06-1999
EP 0210782 A	04-02-1987	AT 62676 T	15-05-1991
		CA 1262726 A1	07-11-1989
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		ES 2000534 A6	01-03-1988
		JP 1608094 C	13-06-1991
		JP 2033705 B	30-07-1990
		JP 62103065 A	13-05-1987
		KR 9403755 B1	30-04-1994
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